REMARKS

Claims 34-51 and 54-61 appear in this application for the Exmaienr's review and consideration. Claim 34 has been amended to incorporate the subject matter of claim 52, support for which is found in paragraphs [0020] to [0022] and [0039] of the published application US 2007/0287949. Claim 34 has been further amended to recite that the apparatus generates a plurality of micro-channels, support for which can be found in claim 53 and in paragraph [0024] of the published application. Claim 34 has been further amended to recite that the polymeric matrix is a hydrophilic polymeric matrix, support for which is found in paragraph [0025] of the published application. Claim 34 has further been amended to recite that the peptide, polypeptide or protein is delivered by diffusion from the patch through the skin to the blood, support for which is found in paragraph [0017] of the published application. Claim 35 has been amended to correct antecedent basis. Claim 38 has been amended to correct a typographical error noted by the Office Action and to recite a preferred polymer, polyvinylpyrrolidone, support for which is found in paragraph [0076] of the published application. Claims 52 and 53 have been cancelled. New claims 55-61 have been added to cover preferred embodiments. Support for claims 55, 56, 60, and 61 is found in paragraph [0086], for claim 57 in paragraph [0071], for claim 58 in paragraph [0078], and for claim 59 in paragraph [0042]. As no new matter has been introduced by any of these changes and additions, their entry at this time is warranted.

Claim Rejections – 35 USC § 112

Claim 38 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is directed to a hydrophilic synthetic polymer selected from the group consisting of a group of sub-genera and accordingly the proper form of the claim should have included an "and" prior to the last sub-genus. As claim 38 has been amended to include the term "and" between "polyvinylalcohol" and "polyurethanes," the rejection has been overcemo and should be withdrawn.

Claim Rejections – 35 USC § 103

Claims 34-54 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,148,232 to Avrahami (referred to hereafter as "Avrahami"), in view of U.S. Patent

No. 6,275,728 to Venkatraman et al. (referred to hereafter as "Venkatraman") in view of U.S. Patent No. 5,983,130 to Phipps et al. (referred to hereafter as "Phipps") in view of U.S. Patent No. 5,418,222 to Song et al. (referred to hereafter as "Song") in view of U.S. Patent No. 5,158,537 to Haak et al. (referred to hereafter as "Haak") in view of U.S. Patent No. 5,906,830 to Farinas et al. (referred to hereafter as "Farinas"). The Office Action states that Avrahami discloses a device that can create micro-channels, then be removed from the skin, and then a commercially available skin patch can be placed over the skin with the micro-channels. The Office Action further states that while Avrahami does not disclose particular skin patches, numerous patents describe electroporation devices and transdermal delivery devices including sustained release transdermal delivery devices. For example, Song discloses single and multiple layer collagen films for sustained release delivery of pharmaceuticals. Venkatraman discloses a hydratable drug reservoir film for electrotransport drug delivery devices. Phipps discloses an electrotransport agent delivery device for delivering a therapeutic agent through a body surface. Farinas discloses transdermal drug delivery systems comprising drug reservoirs wherein polymeric materials which are suitable for such devices include getalin and carrageenan. The Office Action states that it would have been obvious to take the motivational teaching of Avrahami to perform electroporation of the skin followed by placement of a sustained delivery transdermal patch on the electroporated area of the skin.

Applicant respectfully disagrees with the characterizationof the prior art. Avrahami does discloses a device for generating micro-channels in the stratum corneum of the skin, and that the device is then removed from the skin in order to enhance the transdermal delivery of a substance that is subsequently placed on the skin. Avrahami utilizes a commercially available skin patch to supply the substance to be delivered, and such patches do not contain a peptide, polypeptide or protein. Thus, the secondary references are cited.

Venkatraman does not remedy the deficiencies of Avrahami. Venkatraman discloses a hydratable drug reservoir films for electrotransport drug delivery devices (abstract). Venkatraman discloses an electrotransport drug delivery device with drug containing electrode components which are manufactured in an initially free non-hydrated condition but which can be hydrated with drugs (col. 5, lines 19-25 of Venkatraman). As disclosed in Venkatraman, the electrotransport delivry device includes a donor electrode assembly and a counter electrode assembly (col. 6, lines 8-10 of Venkatraman). The donor electrode assembly according to

Venkatraman includes an electrode layer and a reservoir layer containing the agent to be iontophoretically delivered by the device (col. 6, lines 24-27 of Venkatraman). Thus, the electrotransport delivery device of Venkatraman delivers peptides, polypeptides, proteins and macromolecules iontophoretically in a more complicated way than simple diffusion from a patch as claimed in the present application.

In particular, the present invention is a simplified method for the sustained transdermal delivery of a peptide, polypeptide or protein. The present method comprises: generating micro-channels in a region of intact skin of a subject by an apparatus that applies electrical energy to the skin, and then removing the apparatus; affixing a patch to the region of skin where micro-channels are present, the patch comprises a drug reservoir layer which comprises a polymeric matrix and a pharmaceutical composition comprising a peptide, polypeptide or protein; and achieving a therapeutic blood concentration of the peptide, polypeptide or protein for at least 6 hours by diffusion of the peptide, polypeptide or protein from the patch through the skin and into the blood (paragraphs [0035] to [0038] of the present application US 2007/0287949). As claimed, the transdermal delivery of the peptide, polypeptide or protein according to the present invention is achieved by diffusion only. Exudates which diffuse through the micro-channels into the polymeric drug reservoir layer, release the active agent from the drug reservoir layer and deliver it through the micro-channels to the systemic circulation (paragraphs [0017] and [0059] of present application). The transdermal delivery does not involve iontophoresis and the patch is not an electrode patch. In order to clearly distinguish the method recited in claim 34 from the device of Venkatraman, claim 34 has been amended to recite that the delivery of the peptide, polypeptide or protein is by diffusion from the patch through the skin to the blood , support for which is found in paragraphs [0017] and [0059] of present application. Thus, it would not be obvious to one of ordinary skill in the art to combine the teachings of Avrahami and Vekatraman to arrive at the invention of claim 34 as this would involve a much more complicated device and method of application. Therefore, the rejection of claim 34 should be withdrawn. As claims 35, 38, and 39 depend directly or indirectly from claim 34, the rejection of these claims should be withdrawn as well.

Song also does not remedy the deficiencies of Avrahami. Song discloses a collagen film comprising one or two rate controlling layers and one or more drug reservoirs layers (col. 2, lines 18-20 of Song). Song further discloses a method of enhancing wound healing of an epidermal

wound comprising administration of an active ingredient via said collagen film (col. 2, lines 50-55 of Song) and a method of enhancing wound healing of an internal wound comprising administration of an active ingredient via a collagen film having two rate controlling layers (col. 2, lines 55-60 of Song). Song explicitly discloses that the collagen film is useful as a means of delivering the active agent to cells or tissue with which it is in contact (col. 6, lines 19-21 of Song). Thus, according to Song, in the treatment of burns or other traumas to the skin, a collagen film with one rate controlling layer and one backing layer can be placed on the wound to deliver PDGF to the traumatized area (col. 6, lines 21-25 of Song). Song further discloses that collagen films with rate controlling layers at both ends can be used to accelerate healing of surgical wounds so that the film can be placed in the surgical incision and stitched into the wound as an interface between the two surgical wound surfaces (col. 6, lines 27-32 of Song). In the case of delivery of neurotrophic factors, Song discloses that the collagen film can be placed in direct contact with or adjacent to the nerve tissue to be treated with the neurotrophic factor (col. 6, lines 32-36 of Song). Thus, Song explicitly discloses that the collagen films are efficient for local delivery of active agents for wound healing or for the nerve regeneration. Moreover, the collagen films according to Song are effective for delivery of the active agents to the traumatized areas.

In contrast, the method of the present invention comprises the following steps: generating micro-channels in the stratum corneum of a subject by an apparatus that is applied to intact skin, not to a wound or to a traumatized nerve tissue; then affixing a patch to the region where micro-channels are present, with the patch comprising a drug reservoir layer comprising a polymeric matrix and a pharmaceutical composition comprising a peptide, polypeptide or protein; and finally achieving a therapeutic blood concentration of the peptide, polypeptide or protein for at least 6 hours by diffusion of the peptide, polypeptide or protein from the patch through the skin and into the blood (paragraphs [0017], [0035] to [0037] of the published application). It should be emphasized that according to the present invention, prior to application of the apparatus to the skin, the stratum corneum is intact, i.e., the outer layer of the skin (paragraphs [0003], [0017] and [0059]). Thus, one of ordinary skill in the art would not combine the teachings of Avrahami and Song as the collagen films of Song are applied only to tramumatized skin. In order to distinguish the method of the present invention from that of Avrahami in view of Song, claim 34 has been amended to recite that the skin is intact and to include the subject matter of claim 52 so as to recite that the electrodes are in vicinity of the stratum corneum of the skin. Accordingly, claim

52 has been cancelled. Thus, the invention of claim 34 is distinct from Avrahami and Song. As claims 36, 37, 40-43 depend directly or indirectly from claim 34 and include further recitations thereto, these claims are also distinct from Avrahami and Song and the rejection of these claims should be withdrawn.

Haak is another reference that does not remedy the deficiencies of Avrahami, and that is not combinable with Avrahami, Venkatraman, and Song. Haak discloses an iontophoretic drug delivery device with agent containing electrode components. The delivery device includes a multilaminate dry state electrode assembly and a source of electrical power which is electrically connected to the electrode assembly. The electrode assembly includes a reservoir layer comprised of non-hydrated hydratable matrix adapted to contain an agent to be delivered. The electrode assembly also includes an electrode layer in electrical contact with both the power source and the reservoir layer (col. 5, lines 24-39 of Haak). Thus, according to Haak, the drug is delivered iontophoretically by the iontophoretic delivery device (col. 7, lines 25-28 of Haak). This is similar to Venkatraman and results in a complicated process requiring additional equipment to iontophoretically deliver the drug.

In contrast, the present method for sustained transdermal delivery of a peptide, polypeptide or protein comprises a simple delivery by diffusion only. No electrical current is applied to the patch to iontophoretic deliver the peptide, polypeptide or protein. No addtiional equipment is needed for delivery other than the application of a patch to the microchannel containing skin. Furthermore, in order to further clarify the method of the present invention and as indicated above, claim 34 has been amended to recite that the peptide, polypeptide or protein are released from the patch by diffusion, and typically by exudates which diffuse through the micro-channels into the drug reservoir layer of the patch (paragraph [0017] of the published application). As the method of claim 34 is not obvious over Avrahami in view of Venkatraman, Song, and Haak, claims 38, 39, and 41-44 which depend directly or indirectly from claim 34 are not obvious in view of these references.

Farinas is another unrelated reference that does not remedy the deficiency of Avrahami. Farinas discloses a manufacturing method for preparing supersaturated drug reservoirs which involves: (a) admixing a polymeric material and a drug formulation to form a drug-polymer admixture; (b) calculating the depressed melting temperature of the drug-polymer admixrue; (c) heating the admixture to a predetermined temperature effective to dissolve the drug in the

polymeric material, wherein the predetermined temperature is above the depressed melting temperature; and (d) cooling the heated admixture (col. 3, lines 40-52 of Farinas). According to Farinas, the polymeric materials are pressure-sensitive adhesives such as polysiloxanes, polyisobutylenes, polyacrylates, and polyurethanes, preferably acrylates, silicones and polyisobutylenes (col. 6, line 61 through col. 7, line 5 of Farinas). In addition, combinations of acetate-acrylate copolymers with a water-soluble, water-absorptive polymer are preferred materials for reservoirs (col. 7, lines 5-15 of Farinas). The drugs according to Farinas are analgesic serotonergic agonists, narcotic agonists and antagonists, antihistamines, anti-inflammatory agents including NSAID, benzodiazepins, dopaminergic agonists and antagonists, hormones particularly steroids, hormone atagonists, and antipsychotic drugs (col. 7, lines 39-46 of Farinas). Thus, Farinas teaches hydrophobic polymers as drug reservoir materials for non-peptidergic drugs. In order to further clarify the method of the present invention, claim 34 has been amended to recite that the polymeric matrix is a hydrophilic polymeric matrix, support for which is found in paragraph [0025] of the published application. There is no patch in Farinas, nor would his polymers be added to a patch. Thus, if one skilled in the art combines Farinas, Avrahami, Venkatraman and Song, he would not obtain the method for transdermal delivery of a peptide, polypeptide or protein as recited in claim 34 as amended. As claim 34 is not obvious over these references and as claims 46-54 depend directly or indirectly from claim 34 and include further limitations thereto, these claims are not obvious over this combination of references.

Phipps discloses a method of electrotransport drug delivery through a body surface involving the steps of: delivering ionic species by electrotransport at a sufficient current density and over a sufficient period; and thereafter delivering a drug through the body surface (col. 4, lines 22-32 of Phipps). The electrotransport device according to Phipps comprises an anode electrode, a cathode electrode, an anode reservoir and a cathode reservoir, wherein the anode electrode and the cathode electrode are in electrical contact with the drug reservoirs (col. 11, lines 18-20 and 43-45 of Phipps). This is similar to what is disclosed by Venkatraman and Song, and it is quite different from what is claimed. The present method achieves delivery of the peptide, polypeptide or protein by simple diffusion from a patch containing them and does not require additioanl equipemnt for delivery by electrotransport.

In view of the above, Applicants respectfully submit that there is no reason to combine the teachings of the references as suggested in the office action. Under the decision by the Court of Appeals for the Federal Circuit in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), there must be a reason for a person of ordinary skill in the art to combine the elements claimed in order for there to exist a finding of obviousness. In particular, there is no evidence or suggestion in any of the secondary references that the features disclosed therein could be or should be substituted in Avrahami, nor is there any teaching or suggestion that Avrahami is defective and requires improvement. Similarly, there is nothing in Song that suggests that his films could or should be used to transfer an active agent by diffusion into non-traumatized skin. It is also not understood how a skilled artisan would be motivated to use more complicated electrophoretic devices such as those of Venkatraman, Haak or Phipps in place of a simple patch to deliver an active agent. Furthermore, Venkatraman, Haak or Phipps do not require application of their devices to skin that has microchannels. Accordingly, there is no suggestion to combine the teachings and suggestions of secondary references with Avrahami as advanced by the office action except by using Applicants' invention as a template through a hindsight reconstruction of Applicant's claims. See *Ex Parte Crawford et al,* Board Appeal Decision 20062429, Decided May 30, 2007. Accordingly, the obviousness rejection based on the cited combination of references should be withdrawn.

In view of the above, it is respectfully submitted that all current rejections have been overcome and should be withdrawn. Accordingly, the entire application is believed to be in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of this application.

Respectfully submitted,

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